UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Lambda-Cyhalothrin (Karate™). Re-evaluation of 3-Generation Reproduction Study and Necessity for Change of Study on Which RfD is Based

Shaughnessy No. 128867
Tox. Chem. No. 725C
Related Tox. Chem. No. 271F

TO: George Z. Ghali, Manager
RfD/Peer Review Committee
Science Analysis Branch
Health Effects Division (H7509C)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley 8/21/92
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THRU: Roger L. Gardner, Section Head
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Health Effects Division (H7509C) Roger Gardner
8/26/92

The Toxicology Branch (TB-I) has re-evaluated the 3-generation reproduction study conducted on rats with cyhalothrin and has determined that the current NOEL's and LEL's need to be revised as follows:

Reproductive NOEL: 100 ppm (5 mg/kg/day) (HDT)
Parental (systemic) NOEL: 100 ppm (5 mg/kg/day) (HDT)
Developmental NOEL: 100 ppm (HDT)

Although this revision does not affect the RfD value, it does change the study on which that value is based. The RfD value now needs to be based on the 1-year dog study in which the NOEL is 0.5 mg/kg/day and the LEL is 3.5 mg/kg/day, based on clinical signs of neurotoxicity including ataxia, muscle tremors and convulsions.

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Review:

The current RfD for cyhalothrin/lambda-cyhalothrin is based on the NOEL from a 3-generation study conducted on rats with cyhalothrin. In that study, the animals were tested at 0, 10, 30 and 100 ppm in the diet. The NOEL's and LEL's were determined to be as follows:

Reproductive NOEL < 10 ppm based on decreased body weight gain of pups during lactation.

Parental (systemic) NOEL: 10 ppm.

Parental (systemic) LEL: 30 ppm based on reduction in body weights and body weight gains during pre-mating period and during gestation.

Developmental NOEL was combined with the reproductive NOEL at the time when this study was assessed.

TB-I has re-reviewed the study and has determined that all of the NOEL's for each parameter need to be changed to 100 ppm (HDT). The following paragraphs contain a detailed discussion for each of the parameters examined.

Parental/Systemic Toxicity:

The original NOEL and LEL for parental toxicity was based on decreased body weights and body weight gains during the pre-mating and gestation periods. There were no treatment-related mortalities or clinical signs of toxicity. The original Data Evaluation Record (DER) essentially stated that with the exception of those at the lowest dose level, all the decreases in mean body weights and body weight gains that were statistically significant when compared to controls were toxicologically significant. The following tables taken directly from the DER summarize the data. An updated discussion of the data is provided after each table.

Effects of Cyhalothrin on Mean Body Weight Gain (g) During the Premating Period in Rats				
	Dose Level (ppm)			
End of Week	0	10	30	100
F_1 Males				
1	54.7	53.8	53.7	50.5*
6	302.3	297.0	301.7	295.8
12	422.7	414.1	418.8	415.0
F_1 Males				
1	59.3	56.6	57.6	54.9*
6	276.8	271.8	283.5	266.4
11	382.7	351.7*	363.5	349.0*
F_2 Males				
1	61.2	60.3	58.5	56.7
6	287.0	291.7	280.7	264.7
11	385.7	391.5	373.1	352.8*
F_0 Females				
1	40.0	41.0	42.6*	38.3
6	161.2	160.2	165.9	160.3
12	211.5	209.9	219.0*	208.4
F_1 Females				
1	40.6	39.9	40.4	40.4
6	142.7	137.4	134.2*	131.4*
11	182.3	173.2	168.9**	165.1**
F_2 Females				
1	37.6	41.7*	37.6	37.7
6	131.4	135.9	129.0	122.3*
11	166.0	169.0	160.6	156.0*

* Statistically different from control value ($p \leq 0.05$).
** Statistically different from control value ($p \leq 0.01$).

An examination of each of the data points which were statistically significantly less than the control values indicated that not one of the values was less than 90% of the control values. In addition, the decreases in body weight gains were not always consistent across generations in either sex. It is unlikely that any of these decreases are toxicologically significant. One-hundred parts per million (ppm) may be close to the LEL since the NOEL's and the LEL's for the rat subchronic and chronic feeding studies were 50 ppm and 250 ppm, respectively, with decrease in body weight gain as the stated effect.

Effects of Cyhalothrin on Mean Maternal Body Weight (g) and Weight Gain (g) During Gestation in Rats				
	Dose Level (ppm)			
	0	10	30	100
	F_0, Litter A			
Initial Wt.	289.0	288.5	298.6	286.1
Wt. gain at day				
8	23.7	27.5*	26.6	23.0
15	55.7	60.6	58.4	56.0
22	127.2	129.6	132.7	127.6
	F_0, Litter B			
Initial Wt.	328.3	326.5	330.2	323.5
Wt. gain at day				
8	21.6	26.0	25.1	25.2
15	55.2	59.3	60.3	54.5
22	124.4	129.4	143.9**	132.8
	F_1, Litter A			
Initial Wt.	306.3	298.3	282.7**	287.0*
Wt. gain at day				
8	23.4	24.7	23.4	24.0
15	55.3	55.9	53.0	55.4
22	134.5	132.1	130.1	133.2

Effects of Cyhalothrin on Mean Maternal Body Weight (g) and Weight Gain (g) During Gestation in Rats				
	Dose Level (ppm)			
	0	10	30	100
F_1, Litter B				
Initial Wt.	348.3	344.6	321.7**	323.0**
Wt. gain at day				
8	23.9	25.3	20.8	22.0
15	56.1	58.0	51.1	56.7
22	131.3	132.3	120.3	128.2
F_2, Litter A				
Initial Wt.	297.1	296.9	284.6	278.7*
Wt. gain at day				
8	26.3	26.0	26.1	22.4*
15	54.2	56.8	54.1	50.8
22	123.7	124.4	128.5	119.4
F_2, Litter B				
Initial Wt.	331.1	330.9	315.5*	312.4**
Wt. gain at day				
8	23.4	25.5	21.8	20.8
15	53.6	55.5	54.4	50.3
22	142.2	137.0	136.7	127.2*

* Statistically different from control value ($p \leq 0.05$).
** Statistically different from control value ($p \leq 0.01$).

Only two of the values that were statistically significantly less than controls were less than 90% of the control values. These were mean body weight gain in the high dose F_2, Litter B group at day 22 (89.5%), and mean body weight gain at day 8 in Litter A of the F_2 generation (85.2% of control). In general, the values that were statistically significantly less than controls in this table were neither dose-related nor consistent across generations (or the other mating for that generation in

some cases). Again, it is unlikely that any of these decreases are toxicologically significant. Therefore, the parental (systemic) NOEL is re-determined to be 100 ppm (HDT).

Reproductive Toxicity:

The original NOEL for reproductive effects was based on decreases in pup weight gain during lactation, decreases in litter size and decreases in live-born index. These are considered to be developmental effects rather than reproductive effects. There were no treatment-related effects on parental fertility, on precoital interval, on the length of gestation or on maternal neglect. The reproductive NOEL is therefore re-determined to be 100 ppm (HDT).

Developmental Toxicity:

The DER stated that there were statistically significant reductions in litter size for the high dose litters of the F_2A (80% of controls, days 5-29 of lactation) and F_3B (87% of control, days 11-29 of lactation) generations. However, this reduction in litter size was not seen in litters F_2B or in F_3A. It was not consistent. Since the values were between 80-87% of control values, it is possible, as with parental toxicity, that the high dose is close to the LEL for litter size.

The DER stated that there was a decrease in the percentage of live-born pups in the low-dose F_1B and in the mid- and high dose F_3B litters. Again, there was no consistency across other generations or across the other mating group. In addition, these percentages were still within 90% of the control percentages.

Finally, the DER stated that there were decreases in mean pup weights and weight gains during lactation. As with the previous analyses, very few of the statistically significant decreases when compared to the control group were less than 90% of the control values. None of these were consistent between matings for the same generation and the consistency between generations was limited. It is unlikely that these decreases are toxicological effects, although it is again possible, as with parental toxicity, that the high dose is close to the LEL for pup weights and weight gains during the lactation period. The NOEL for developmental toxicity is re-determined to be 100 ppm. The following table summarizes the data.

Effects of Cyhalothrin on Mean Initial Pup Body Weight (g) and Weight Gain (g) in Rats				
	Dose Level (ppm)			
Weight Gain	0	10	30	100
	F_1A Females			
Initial Wt.	5.4	5.7	5.7	5.7
Postnatal Day				
5	2.9	2.3*	2.5	2.5
11	11.3	10.6	10.7	10.5
22	32.4	30.8	30.9	31.1
29	61.6	59.9	61.1	59.8
	F_1A Males			
Initial Wt.	5.8	6.2	6.1	6.1
Postnatal Day				
5	2.9	2.6	2.8	2.7
11	12.1	11.4	11.5	11.0
22	34.2	33.1	32.3	34.0
29	67.0	65.9	65.9	66.6
	F_1B Females			
Initial Wt.	5.9	6.0	5.9	5.9
Postnatal Day				
5	2.5	3.0	2.7	2.5
11	11.8	12.5	11.4	10.8
22	36.6	37.1	32.9*	33.2*
29	67.3	68.8	61.8*	62.2*

Effects of Cyhalothrin on Mean Initial Pup Body Weight (g) and Weight Gain (g) in Rats				
	Dose Level (ppm)			
Weight Gain	0	10	30	100
	F1B Males			
Initial Wt.	6.2	6.4	6.3	6.0
Postnatal Day				
5	2.6	3.1	3.0	2.5
11	11.9	13.0	12.0	11.4
22	37.5	38.5	35.2	34.8
29	71.2	72.9	66.8	66.4*
	F_2A Females			
Initial Wt.	5.8	5.9	5.8	5.8
Postnatal Day				
5	3.3	3.1	3.0	3.0
11	12.6	12.4	12.2	12.7
22	36.7	36.9	33.6	36.5
29	69.0	70.8	67.6	70.0
	F_2A Males			
Initial Wt.	6.1	6.2	6.2	6.2
Postnatal Day				
5	3.2	3.1	2.9	3.3
11	13.1	12.6	12.4	13.6
22	37.1	36.7	35.3	38.9
29	71.8	73.2	72.5	75.8

Effects of Cyhalothrin on Mean Initial Pup Body Weight (g) and Weight Gain (g) in Rats				
	Dose Level (ppm)			
Weight Gain	0	10	30	100
	F_2B Females			
Initial Wt.	6.0	5.9	6.0	6.0
Postnatal Day				
5	2.6	2.8	3.3	2.7
11	12.4	12.8	13.9	12.1
22	37.9	39.2	38.5	36.6
29	72.5	72.6	73.6	70.4
	F_2B Males			
Initial Wt.	6.5	6.6	6.4	6.3
Postnatal Day				
5	2.9	2.9	3.4	2.7
11	13.5	13.4	14.2	12.2
22	41.0	41.8	41.0	37.4*
29	80.1	79.4	80.0	73.9*
	F_1A Females			
Initial Wt.	5.8	5.7	5.7	5.8
Postnatal Day				
5	3.2	3.0	2.9	2.9
11	13.3	12.8	12.2	11.7*
22	38.5	36.5	34.7**	34.7*
29	73.7	71.2	67.8**	67.6**

Effects of Cyhalothrin on Mean Initial Pup Body Weight (g) and Weight Gain (g) in Rats				
	Dose Level (ppm)			
Weight Gain	0	10	30	100
	F_1A Males			
Initial Wt.	6.2	6.2	6.1	6.1
Postnatal Day				
5	3.4	3.1	2.9*	2.9*
11	14.0	12.1**	12.4*	11.7**
22	39.8	37.1*	35.8**	34.8**
29	79.1	75.2	72.1**	69.9**
	F_1B Females			
Initial Wt.	6.0	6.2	6.1	5.9
Postnatal Day				
5	3.4	3.3	3.3	3.5
11	13.7	12.8	13.4	13.3
22	39.3	36.9	37.0	37.7
29	74.7	70.8	70.4*	71.9
	F_1B Males			
Initial Wt.	6.4	6.5	6.4	6.4
Postnatal Day				
5	3.6	3.4	3.3	3.4
11	14.3	13.6	13.0*	13.4
22	40.9	39.0	37.6*	38.4
29	80.0	76.4	74.1*	75.7

* Statistically different from control value ($p \leq 0.05$).
** Statistically different from control value ($p \leq 0.01$).

Caswell No. 725C | File Last Updated _____ | Current Date 8/21/92

Chemical Name Cyhalothrin

Shaughnessy No.: 128867

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Reproduction-3 generation. Species: rat. ICI Central Tox. Lab. CTL/P/906	Cyhaloth rin batch ADM/4615 680	073207-073209	Update: Reproductive NOEL: 100 ppm (HDT). Maternal NOEL: 100 ppm (HDT). Developmental NOEL: 100 ppm (HDT)	N/A	Guideline 005957

1 - Liner Update: Reproduction Study

005957

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS

CASWELL# 725C

TOXCHEM NO. 12886/ Cyhalothrin

FILE LAST PRINTED: 08/21/92

CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
Developmental Toxicity Study Species: rat Hazleton Labs, Europe 0170; 6/81	Cyhalothrin batch 005, 89.25% pure w/w.	073206	Levels tested by gavage in Charles River SPF CD strain: 0, 5, 10 & 15 mg/kg/day. Maternal NOEL = 10 mg/kg/day. Maternal LEL = 15 mg/kg/day. (reduced body wt. and food consumption). Fetotoxic NOEL > 15 mg/kg/day Teratogenic NOEL > 15 mg/kg/day. Developmental NOEL => 15 mg/kg/day HDT A/D ratio = 10/15 = 0.7		Minimum 005100
Developmental Toxicity Study Species: rabbit Hazleton Labs, Europe RB 0169; 6/81	Cyhalothrin batch 005 89.2%	073206	Levels tested by gavage in N.Z.W. str. Maternal NOEL = 10 mg/kg Maternal LEL = 30 mg/kg (decr. in body weight gain). Developmental NOEL = 30 mg/kg. A/D ratio = 10/30 = 0.33		Minimum 005100
Reproduction-3 generation Species: rat ICI Central Tox. Lab. CTL/P/906; 5/15/84	Cyhalothrin batch ADM/ 4615680. 89.2% pure w/w	073207- 073209	Levels tested in SPF Wistar strain: 0, 10, 30 & 100 ppm. Reproductive NOEL < 10 ppm (LDT). (decr. body weight gain during weaning) Maternal NOEL = 10 ppm. Maternal LEL = 30 ppm (reduced body weight gain during pregnancy).		Guideline 005100 005161